

issues. This is very different to the “better than 95%” accuracy stated by Smith in his testimonial on behalf of USCOM Ltd ([http://www.uscom.com.au/benefits/test\\_brendan.html](http://www.uscom.com.au/benefits/test_brendan.html) [accessed Apr 2010]).

We appropriately used correlation to assess percentage changes in CO, as these are dimensionless units.

We believe the concerns of Smith and Madigan about the competence of the USCOM operator are addressed above. It is pertinent to note that in response to the question “Is it easy to use?”, Smith stated: “My grand daughter is six years old and she can use it. It really is child’s play” ([http://www.uscom.com.au/benefits/test\\_brendan.html](http://www.uscom.com.au/benefits/test_brendan.html) [accessed Apr 2010]). We maintain that our results and a balanced review of the current peer reviewed literature support the conclusion of our study.

\**Editor’s note:* the letter by Phillips that Boyle and colleagues respond to here was an earlier draft of the one published above.

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## ECMO: expertise and equipoise

Graeme MacLaren

**TO THE EDITOR:** Moran and colleagues should be congratulated on publishing their thought-provoking critique of the evidence for extracorporeal membrane oxygenation (ECMO) in adult respiratory failure.<sup>1</sup> They concluded that there was sufficient uncertainty about its effectiveness to mandate further randomised controlled trials. To some extent, this point of view had been anticipated by the editorialists of the CESAR (Conventional Ventilation or ECMO for Severe Adult Respiratory Failure) study, who commented that the trial would provide ammunition for advocates and detractors of ECMO alike.<sup>2</sup>

One issue that was not addressed in the updated meta-analysis or the accompanying editorial<sup>3</sup> was the question who should be conducting these further studies. The trials cited in the meta-analysis that pre-dated the CESAR study have been heavily criticised for involving institutions that had inadequate experience with this technically complex area of life support. In the CESAR study, all patients randomised to the ECMO arm were transferred to an institution that was very experienced with ECMO, where

the clinicians could then use it at their discretion or continue their own, unspecified form of conventional care.<sup>4</sup> This raised the question of whether the treatment effect was due to ECMO or other factors, such as the effectiveness of conventional care in the non-ECMO patients being treated outside of Glenfield Hospital. An alternative approach that would avoid this problem would be to randomise patients already admitted to an institution capable of and experienced with ECMO to either ECMO or control. In other words, the availability of ECMO would be determined by a protocol and a randomisation process, not by a clinician.

However, vanishingly few clinicians that could lay some claim to be expert in ECMO would agree to such a protocol. Those with the requisite skills and experience to properly conduct a scientifically rigorous, randomised trial of ECMO would be unlikely to have sufficient equipoise to participate. In my experience, familiarity begets advocacy. Conversely, it is nearly impossible to conduct an ethically appropriate and scientifically unas-

sailable study when patients near death are randomised to a trial of rescue mechanical life support,<sup>5</sup> which inevitably leads to arguments such as those mustered by Moran and colleagues casting doubt on the quality of the evidence. It is perhaps time to acknowledge that, for many clinicians, the debate about the effectiveness of ECMO in adult respiratory failure will never be convincingly resolved.

If further parallels are needed, it may also be worthwhile reflecting on the absence of scientific evidence in other areas of critical care. Where are the randomised controlled trials demonstrating the effectiveness of continuous renal replacement therapy over placebo in acute renal failure, or prospective evidence that intravenous catecholamines improve outcomes in septic shock?

In their conclusions, Moran and colleagues reiterate an important point: “the average treatment effect is not the effect of treatment for each individual”. The efficacy of ECMO when correctly applied to an appropriate patient is

self-evident. The key question is not “Does it work?”, but rather, “Exactly when, how, and in whom do we use it?”

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John L Moran, Richard P Chalwin and Petra L Graham

**IN REPLY:** Our recent “Point of View” article<sup>1</sup> in the Journal, reconsidering the role of extracorporeal membrane oxygenation (ECMO), has generated responses by Pellegrino and Davies<sup>2</sup> and MacLaren.<sup>3</sup> We comment on each of these responses in turn.

Pellegrino and Davies posed the question, “To what extent has the CESAR trial justified a role for ECMO support in patients with severe acute respiratory failure, and particularly acute respiratory distress syndrome (ARDS)?” By way of answer, they first considered the results of our updated quantitative meta-analysis and then offered further reflection on the “the place of ECMO for respiratory failure in 2010”.

With respect to the results of our updated quantitative meta-analysis, we certainly do not resile from this meta-analysis, as it represents a pertinent summary of what is accepted as generating unbiased estimates of a therapeutic intervention: the randomised controlled trial (RCT). We noted the small trial numbers, the long time span of the trials and the modest degree of heterogeneity. We suggested that our Bayesian approach was apposite for this scenario and concluded that, on the basis of the available RCT evidence, a null effect of ECMO was not excluded, and that, compared with standard care, there was only weak evidence for efficacy.

Given these cautions, we may ask, “Is this is the only evidence?” Certainly not. Firstly, as we noted, the body of observational data suggested otherwise; but importantly,

did *not* provide estimates of use effectiveness or method effectiveness in the strict sense.<sup>1</sup> Secondly, there remains the possibility of evidence synthesis, most appropriately, we suggest, from a Bayesian perspective,<sup>4</sup> using both randomised and non-randomised studies. However, as we have previously noted,<sup>5</sup> there appear to be no appropriate (case-control) studies available for such an analysis.

This is a matter of some importance. Mitchell and colleagues, in a recent systematic review of ECMO<sup>6</sup> and analysing the same three RCTs as in our updated meta-analysis,<sup>1</sup> arrived at similar pooled mortality estimates and conclusions. They further discussed three earlier cohort studies (also identified in our previous review<sup>5</sup>) and the ANZ ECMO Influenza Investigators report of 68 patients from 15 intensive care units,<sup>7</sup> but were unable to include these studies in their quantitative analysis, as they reported no appropriately matched controls. That the ANZIC Influenza Investigators<sup>8</sup> reported ventilation of 456 patients admitted to 104 Australian ICUs in the same 2009 H1N1 influenza pandemic indicates the potential for such a matched outcome comparison.

With respect to “the place of ECMO for respiratory failure in 2010”, Pellegrino and Davies rightly point to difficulties in the assessment of complex care processes such as ECMO and medical emergency teams. But such a caution seems problematic when we subsequently read that a French-led multicentre trial of ECMO is due to commence. The introduction of intuitively reasonable

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complex care processes has as its corollary an inevitable consequence — that of broadening patient populations considered appropriate for ECMO.<sup>2</sup> We have previously documented health policy concerns about the status of ECMO leading to the conduct of the CESAR trial.<sup>5</sup> In the absence of convincing evidence from the CESAR trial, the question remains: what are the most appropriate tools to determine the efficacy of ECMO?<sup>2</sup> After 44 years of use, the case for ECMO (as with steroids in sepsis and saline versus colloid in fluid resuscitation) must embody appropriately conducted RCTs rather than more uncontrolled observational data. The conduct of such debate in the absence of any jurisdictional economic evaluation<sup>9</sup> of ECMO seems particularly ill-advised.

MacLaren rightly points out the absence of scientific evidence in other areas of critical care for certain interventions such as continuous renal replacement therapy, and, more importantly, with respect to complex care processes, that “familiarity begets advocacy”. However, we would reverse his two final questions: we apparently know, with some caveats, “when, how, and in whom” to apply the process, but the simple question “Does it work?” seems, to our mind, not to have been appropriately answered.

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